(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 July 2003 (10.07.2003)

PCT

(10) International Publication Number
WO 03/055865 A1

(51) International Patent Classification[7]: C07D 239/88, A61K 31/517, A61P 37/00

(21) International Application Number: PCT/JP02/13286

(22) International Filing Date:
19 December 2002 (19.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PR9756 24 December 2001 (24.12.2001) AU

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

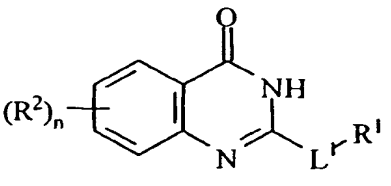
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/055865 A1

(54) Title: QUINAZOLINONE DERIVATIVE



(I)

(57) Abstract: A quinazolinone derivatives having poly (adenosine 5'-diphospho-ribose) polymerase (PARP) inhibitory activity represented by the formula (I): wherein R^1 is substituted cyclic amino groups or optionally substituted amino group, R^2 is substituent, n means an integer of 0 to 4, and $L^1$is (1) cyclo (lower) alkylene, (2) cyclo (lower) alkenylene, (3) diradical of saturated- or unsaturated monocyclic group with one or more nitrogen atom(s), which is obtained after removal of one hydrogen atom from said monocyclic group, or (4) -N (R^3) -L^2- (wherein R^3 is hydrogen or lower alkyl, and L^2 is lower alkylene or lower alkenylene), or its prodrug, or a salt thereof.

DESCRIPTION

Quinazolinone Derivative

Technical Field

This invention relates to a novel quinazolinone derivative having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

Background Art

Poly(adenosine 5'-diphospho-ribose)polymerase ["poly(ADP-ribose)polymerase" or "PARP", which is also sometimes called "PARS" for "poly(ADP-ribose)synthetase"] is an enzyme located in the nuclei of cells of various organs, including muscle, heart and brain cells. PARP plays a physiological role in the repair of strand breaks in DNA. Once activated by damaged DNA fragments, PARP catalyzes the attachment of up to 100 ADP-ribose units to a variety of nuclear proteins, including histones and PARP itself.

Some quinazolinone derivatives having inhibitory activity of PARP have been known, for example, in WO95/24379, WO98/33802 and WO99/11624.

Disclosure of the Invention

This invention relates to a novel quinazolinone compound, which has pharmaceutical activity such as PARP inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

One object of this invention is to provide the novel quinazolinone compound, which has a PARP inhibiting activity.

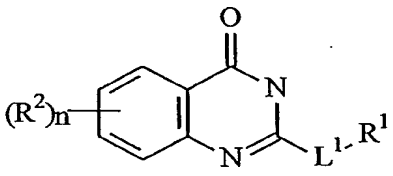
Another object of this invention is to provide a process

for production of the quinazolinone compound.

A further object of this invention is to provide a pharmaceutical composition containing the quinazolinone compound as an active ingredient.

Still further object of this invention is to provide a use of the quinazolinone compound for manufacturing a medicament for treating or preventing various diseases, or a method of treating or preventing various diseases by administering the quinazolinone compound in an effective amount to inhibit PARP activity.

The quinazolinone compound of this invention can be represented by the following formula (I):



(I)

[wherein R^1 is substituted cyclic amino groups, optionally substituted carbocyclic group or optionally substituted amino group,

R^2 is substituent,

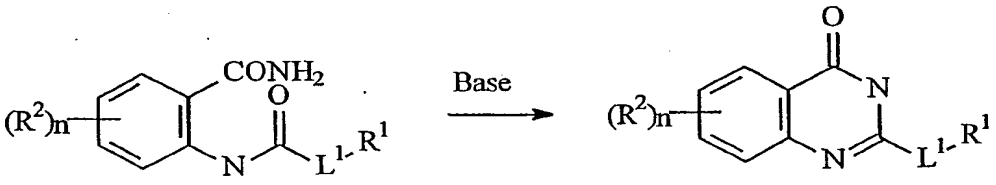
n means an integer of 0 to 4, and

L^1 is (1) cyclo(lower)alkylene, (2) cyclo(lower)alkenylene, (3) diradical of saturated- or unsaturated monocyclic group with one or more nitrogen atom(s), which is obtained after removal of one hydrogen atom from said monocyclic group, or (4) $-N(R^3)-L^2-$ (wherein R^3 is hydrogen or lower alkyl, and L^2 is lower alkylene or lower alkenylene)],

or its prodrug, or a salt thereof.

The compound (I) or its prodrug, or a salt thereof can be prepared by the following processes. In the following formulae, the compounds may be prodrugs or their salts.

Process 1



(II)
or a salt thereof

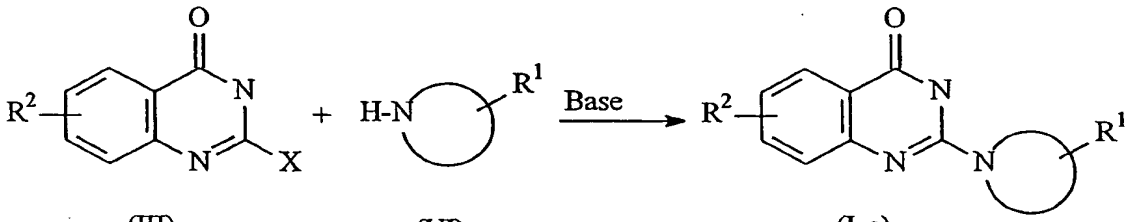
(I)
or salt thereof

[wherein, R^1, R^2, n and L^1 are each as defined above.]

In this process, the compound (I) or a salt thereof can be produced by subjecting the compound (II) to cyclization reaction in the presence of base, such as inorganic bases, for example, an alkali metal [e.g., sodium or potassium], alkoxide, hydroxide, carbonate or bicarbonate thereof, or organic bases such as a trialkylamine [e.g., trimethylamine or triethylamine] or the like.

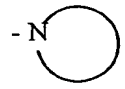
The reaction is usually carried out in a conventional solvent such as water, an alcohol (e.g., methanol, ethanol or isopropyl alcohol), ether, tetrahydrofuran, dioxane, diethylether, amide (e.g., N,N-dimethylformamide, N,N-dimethylacetamide), nitrile (e.g., acetonitrile), or any other organic solvent which does not adversely affect the reaction. The reaction may be usually carried out under cooling to heating since the reaction temperature is not critical.

Process 2



(III) or a salt thereof (VI) or a salt thereof (I-a) or a salt thereof

[wherein, X is leaving group,



is saturated- or unsaturated monocyclic group with one or more nitrogen atom(s), and R^1 and n are each as defined above.]

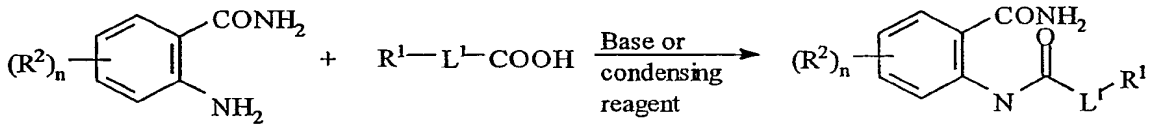
In this process, the compound (I-a) or a salt thereof can be produced by reacting the compound (III) or a salt thereof and compound (VI) or a salt thereof in the presence of base, such as inorganic bases, for example, an alkali metal [e.g., sodium or potassium], alkoxide, hydroxide, carbonate or bicarbonate thereof, or organic bases such as a trialkylamine [e.g., trimethylamine or triethylamine] or the like.

The reaction is usually carried out in a conventional solvent such as an alcohol (e.g., methanol, ethanol or isopropyl alcohol), tetrahydrofuran, dioxane, diethylether, amide (e.g., N,N-dimethylformamide, N,N-dimethylacetamide), nitrile (e.g., acetonitrile), or any other organic solvent which does not adversely affect the reaction. The reaction may be usually carried out under cooling to heating since the reaction temperature is not critical.

The compounds of the present invention can be purified by any conventional purification methods employed for purifying organic compounds, such as recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography and the like. The compounds can be identified by conventional methods such as NMR spectrography, mass spectrography, IR spectrography, elemental analysis, and measurement of melting point.

Some of the starting compounds (II) or a salt thereof are novel and can be prepared by the well-known processes or its analogous processes, for example, the processes described in the J. Med. Chem. 1998, 41, 5247-5256 and J. Org. Chem., 21, 478- (1956). The following process is given as an example.

Reference Process 1



or its reactive derivative at the amino group, or a salt thereof

or its reactive derivative at the carboxy group, or a salt thereof

(II)
or a salt thereof

[wherein, R^1, R^2, n and L^1 are each as defined above.]

Suitable salt of the compound (I) of the present invention are pharmaceutically acceptable conventional non-toxic salts and can be an organic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, oxalate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.), an inorganic acid

addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. aspartic acid salt, glutamic acid salt, etc.), or the like.

The "prodrug" means the derivative of compound of the present invention having a chemically or metabolically degradable group, which becomes pharmaceutically active after biotransformation.

The compound (I) of the present invention may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. Further more certain the compound (I) which contains alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compound (I) may also exist in tautomeric forms, and the invention includes both mixtures and separate individual tautomers.

The compound (I) or a salt thereof can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably includes a hydrate or an ethanolate.

The radiolabelled derivative of the compound (I), which is suitable for biological studies, may be included in the scope of invention.

In the above and subsequent description of the present specification, suitable examples and illustrations of the various definitions, which the present invention includes within the scope thereof, are explained in detail as follows.

The term "lower" means a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" includes a straight or branched alkyl having 1 to 6 carbon atom(s), in particular 1 or 2 carbon atom(s).

Preferable examples which may be mentioned are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl.

Suitable "lower alkoxy" includes straight or branched alkoxy having 1 to 6 carbon atom(s), in particular 1 or 2 carbon atom(s). Preferable examples which may be mentioned are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy and tert-butoxy, preferably methoxy.

Suitable "lower alkylamino" include mono(lower)alkylamino and di(lower)alkylamino. Preferable examples which may be mentioned are methylamino, dimethylamino, ethylamino, dimethylamino, n-propylamino, isopropylamino, n-butylamino, iso-butylamino, sec-butylamino and tert-butylamino, preferably dimethylamino and diethylamino.

Suitable "aryl" may be intended to mean a mono-, di- or polynuclear aromatic radical having preferably 6 to 12 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl, indenyl, indanyl (1,2-dihydroindenyl), fluorenyl and the like, preferably phenyl or naphthyl.

The term "halogen" means fluoro, chloro, bromo or iodo.

Suitable "halo(lower)alkyl" contains 1 to 4 carbon atom(s), in particular 1 or 2 carbon atom(s), and 1 to 9 halogen atom(s), in particular 1 to 5 identical or different halogen atom(s), preferably fluorine, chlorine and bromine, in particular fluorine and chlorine. Preferable examples which may be mentioned are trifluoromethyl, trichloromethyl, chlorodifluoromethyl, dichlorofluoromethyl, chloromethyl, bromomethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl and pentafluoroethyl, preferably trifluoromethyl.

The term "carbocyclic group" is intended to mean

cyclo(lower)alkyl or cyclo(lower)alkenyl.

Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl moiety" in the term "cyclo(lower)alkylene" includes a saturated carbocycle having 3 to 7 carbon atoms, in particular 5 to 6 carbon atoms. Preferable examples which may be mentioned are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, preferably cyclopropyl and cyclohexyl (e.g., 1,3- cyclohexylene, 1,4-cyclohexylene, etc.).

Suitable "cyclo(lower)alkenyl" and "cyclo(lower)alkenyl moiety" in the term "cyclo(lower)alkenylene" includes a partially saturated carbocycle having 3 to 7 carbon atoms, in particular 5 to 6 carbon atoms. Preferable examples which may be mentioned are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl, preferably cyclopentenyl and cyclohexenyl.

Preferable example which may be mentioned as "cyclo(lower)alkylene" are cyclopentenylene (e.g., 1,3-cyclocyclopent-1-enylene, etc.), cyclohexenylene (e.g., 1,3-cyclohex-1-enylene, etc.).

Suitable "heteroaryl" and "heteroaryl" moiety in the terms "heteroaryl(lower)alkyl" and "heteroaromatic acyl" is intended to mean 5- to 7-membered rings having preferably 1 to 3 heteroatom(s), in particular 1 or 2 identical or different heteroatom(s). Heteroatoms in the heteroaryl are oxygen, sulfur or nitrogen. Examples which may be mentioned are furyl, thienyl, pyrazolyl, imidazolyl, triazolyl (e.g., 1,2,3- and 1,2,4-triazolyl, etc.), isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl (e.g., 1,3,4-, and 1,2,5-oxadiazolyl, etc.), azepinyl, pyrrolyl, pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl (e.g., 1,3,5-, 1,2,4- and 1,2,3-triazinyl, etc.), oxazinyl (e.g., 1,2,4- and 1,2,6-oxazinyl, etc.), oxepinyl, thiepinyl and diazepinyl

(e.g., 1,2,4-diazepinyl, etc.), preferably thienyl, pyrazolyl, imidazolyl, thiazolyl, pyridinyl and pyrazinyl.

Suitable "cyclic amino group" are heteroaromatic or aliphatic ring systems having one or more nitrogen atoms as the heteroatom, in which the heterocyclic rings can be saturated or unsaturated, can be one ring system or several fused ring systems, and optionally contain further heteroatoms, such as nitrogen, oxygen and sulfur and the like. Cyclic amino groups can furthermore also denote a spiro ring or a bridged ring system. The number of atoms which form cyclic amino groups is not limited, for example in the case of a single-ring system, they comprise 3 to 8 atoms, and in the case of a three-ring system, they comprise 7 to 11 atoms.

Preferable examples of "cyclic amino group" are described as follows:

(1) examples which may be mentioned of cyclic amino group with saturated monocyclic groups with one or more nitrogen atom(s) as the heteroatom are azetidinyl (3-azetidinyl), pyrrolidinyl (e.g., 1- and 3-pyrrolidinyl, etc.), piperidyl (e.g., 1- and 4-piperidyl, etc.), homopiperidino (e.g., hexahydro-1H-azepin-1-yl, etc.), homopiperazinyl (e.g., hexahydro-1H-1,4-diazepin-1-yl, etc.), imidazolidinyl (e.g., 1-imidazolidinyl, etc.), piperazinyl (e.g., 1-piperazinyl, etc.), perhydropyrimidinyl (e.g., perhydropyrimidin-1-yl, etc.) and diazacycloheptanyl (e.g., 1,4-diazacycloheptan-1-yl, etc.);

(2) examples which may be mentioned of cyclic amino group with unsaturated monocyclic groups with one or more nitrogen atom(s) as the heteroatom are pyrrolinyl (e.g., 2-pyrrolin-1-yl, etc.), pyrrolyl (e.g., 1-pyrrolyl, etc), tetrahydropridinyl (e.g., 3,6-dihydro-1(2H)-pyridinyl, etc.), pyridinyl (e.g., 2-pyridinyl, etc.), tetrahydroazepinyl (e.g.,

2,3,6,7-tetrahydro-1H-azepin-1-yl, 2,3,4,7-tetrahydro-1H-azepin-1-yl, etc.), imidazolyl (1-imidazolyl), pyrazolyl, triazolyl, tetrazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, dihydro-pyridazinyl (e.g., 1,2-dihydro-pyridazin-1-yl, etc.) and dihydro-pyrimidinyl (e.g., 1,2-dihydro-pyrimidin-1-yl, etc.);

(3) examples which may be mentioned of cyclic amino groups with saturated and unsaturated monocyclic groups with 1 to 3 nitrogen atom(s) and 1 or 2 sulfur atom(s) as heteroatoms are thiazolidinyl (e.g., 3-thiazolidinyl, etc.), isothiazolinyl (e.g., 2-isothiazolinyl, etc.) and thiomorpholino;

(4) examples which may be mentioned of cyclic amino groups with saturated and unsaturated monocyclic groups with 1 to 3 nitrogen atom(s) and 1 or 2 oxygen atom(s) as heteroatoms are oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, and 1,3,4-oxadiazolyl) or morpholinyl;

(5) examples which may be mentioned of cyclic amino groups with saturated and unsaturated fused cyclic groups are indolyl (e.g., 1-indolyl, etc.), dihydrobenzimidazolyl (e.g., 1,2-dihydrobenzimidazol-1-yl, etc.), perhydropyrrolo[1,2-a]pyrazinyl (e.g., perhydropyrrolo[1,2-a]pyrazin-2-yl, etc.), tetrahydrobenzo[f]isoquinolinyl (e.g., 1,4,5,6-tetrahydrobenzo[f]isoquinolin-3(2H)-yl, etc.), hexahydrobenz[f]isoquinolinyl (e.g., cis- and trans-1,4,4a,5,6,10b-hexahydrobenz[f]isoquinolin-3(2H)-yl, etc.), tetrahydropyrido[3,4-b]indolyl (e.g., 1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl, etc.) tetrahydrobenzazepinyl (e.g., 1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl, etc.)

dihydroisoquinolinyl (e.g., 3,4-dihydro-2(1H)-isoquinolinyl, etc.);

(6) examples which may be mentioned of cyclic amino groups with spirocyclic groups are azaspiro[4,5]decanyl (e.g., 2-azaspiro[4,5]decan-2-yl, etc.), spiro[1H-indene-1,4'-piperidinyl] (e.g., spiro[1H-indene-1,4'-piperidin-1'-yl], etc.), and dihydrospiro[1H-indene-1,4'-piperidinyl] (e.g., 2,3-dihydrospiro[1H-indene-1,4'-piperidin-1'-yl], etc.);

(7) examples which may be mentioned of cyclic amino groups bridged heterocyclic groups are azabicyclo[2,2,1]heptanyl (e.g., 2-azabicyclo[2,2,1]heptan-7-yl, etc.) and diazabicyclo[2.2.1]heptyl (e.g., 2,5-diazabicyclo[2.2.1]hept-2-yl, etc.).

Among the above, preferable "cyclic amino group" included in R^1 is above-mentioned (1) or (2), in which the most preferable one may be piperidinyl, tetrahydropyridinyl and piperazinyl.

Preferable examples which may be mentioned of "diradical of saturated or unsaturated monocyclic group with one or more nitrogen atom(s), which is obtained after removal of one hydrogen atom from said monocyclic group" are azetidinylene (e.g., 1,2- or 1,3-azetidinylene), pyrrolidinylene (e.g., 1,2- or 1,3-pyrrolidinylene), piperidinylene (e.g., 1,3- or 1,4-piperidinylene).

It has been known that, during major cellular stresses, the activation of PARP can rapidly lead to cell damage or death through depletion of energy stores and PARP activation play a key role in both NMDA- and NO-induced neurotoxicity (Zhang et. al., Science, 263: 687-89 (1994)). Therefore, the compound possessing PARP

inhibiting activity, such as the compound (I) or a pharmaceutically acceptable salt thereof of this invention is useful in treating and preventing various diseases ascribed by NMDA- and NO-induced toxicity. Such diseases include, for example, tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke; Alzheimer's disease; Parkinson's disease; epilepsy; Amyotrophic lateral Scleosis (ALS); Huntington's disease; schizophrenia; chronic pain; ischemia and neuronal loss following hypoxia; hypoglycemia; ischemia; trauma; and nervous insult.

It has been demonstrated that PARP inhibitor are useful in deducing infarct size (Thiemermann et al, Proc. Natl. Acad. Sci. USA, 94: 679-83 (1997)). Therefore, the compound possessing PARP inhibiting activity, such as the compound (I) or a pharmaceutically acceptable salt thereof of this invention is useful in treatment and prevention of previously ischemic heart or skeleton muscle tissue.

It is also known that PARP is thought to play a role in enhancing DNA repair. So, the compound possessing PARP inhibiting activity, such as the compound (I) or a pharmaceutically acceptable salt thereof of this invention is effective in treating and preventing radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy.

Further, the compound possessing PARP inhibiting activity, such as the compound (I) or a pharmaceutically acceptable salt thereof of this invention is useful in extending the life-span and proliferative capacity of cells and altering gene expression of senescent cells. It is useful for treating and preventing skin

aging; Alzheimer's diseases; arteriosclerosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescence diseases.

Still further, the compound possessing PARP inhibiting activity, such as the compound (I) or a pharmaceutically acceptable salt thereof of this invention is effective in treating and preventing inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and tumor. Also, it is useful in reducing proliferation of tumor cells and making synergistic effect when tumor cells are co-treated with an alkylamine drug.

The compound possessing PARP inhibiting activity, such as the compound (I) of this invention or a pharmaceutically acceptable salt thereof of this invention is effective in treating and preventing pituitary apoplexy; conjunctivitis; retinoblastoma; retinopathy; acute retinal necrosis syndrome; Sjogren's syndrome.

The compound (I), its prodrug, or a salt thereof can be administered alone or in the form of a mixture, preferably, with a pharmaceutical vehicle or carrier.

The active ingredient of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains a compound (I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external (topical), enteral, intravenous, intramuscular, parenteral or intramucous applications. The active ingredient can be formulated, for example, with the conventional non-toxic, pharmaceutically acceptable carriers for ointment, cream, plaster, tablets, pellets, capsules,

suppositories, solution (saline, for example), emulsion, suspension (olive oil, for example), aerosols, pills, powders, syrups, injections, troches, cataplasms, aromatic waters, lotions, buccal tablets, sublingual tablets, nasal drops and any other form suitable for use. The carriers which can be used are water, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paster, magnesium trisilicate, talc, corn starch, keratin, paraffin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in a pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

The active ingredient can be formulated into, for example, preparations for oral application, preparations for injection, preparations for external application, preparations for inhalation, preparations for application to mucous membranes.

Mammals which may be treated by the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans, preferably humans.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose to a human patient of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg, and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

In order to illustrate the usefulness of the object compound

(I), the pharmacological test data of the compound (I) are shown in the following.

(1) Test Compound:

Compound A:

2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)-1-cyclopenten-1-yl]-4(3H)-quinazolinone (The compound of Example 2-4)

Compound B:

2-[4-(4-Phenyl-3,6-dihydro-1(2H)-pyridinyl)-1-piperidinyl]-4(3H)-quinazolinone (The compound of Example 6-3)

PARP inhibitory activity (In vitro assay)

(2) Assay conditions:

The recombinant human PARP (5.3mg protein/ml) were incubated with a test compound in a 100μl reaction buffer containing the indicated concentration of 1 mCi/ml ^{32}P-NAD, 50mM Tris-HCl, 25mM $MgCl_2$, 1mM DTT (dithiothreitol), 0.05mM NAD (nicotinamido adenine dinucleotide), 1mg/ml activated DNA, pH8.0. Incubation was for 15 minutes at a room temperature and the reaction was stopped by the addition of 200μl of ice-cold 20% trichloroacetic acid followed by rapid filtration through GF/B filters. The filters were treated with scintillation fluid and acid-insoluble counts were measured for quantification of unit activity.

PARP inhibitory activity (%) =

[1-(enzyme activity with test compound)/(enzyme activity with vehicle)] x100

(3) Result

PARP inhibitory activity (IC_{50}) in test compound.

Test Compound	IC50 (μM)
Compound A	< 0.5
Compound B	< 0.5

This invention relates to novel Quinazolinone compounds had a potent PARP inhibitory activity. PARP inhibitors including this invention relates to novel quinazolinone compounds were effective in preventing reduction of striate DA and its metabolite induced by MPTP treatment in mice. Therefore, it suggests that these compounds may have protective benefit in the treatment of neurodegenerative disease such as Parkinson's disease.

Abbreviations used herein have the following meanings:

ABBREVIATION	:	DEFINITION
Me	:	methyl
Et	:	ethyl
TBu	:	tert-buthyl
Bzl	:	benzyl
Ph	:	phenyl
Ac	:	acetyl
Bz	:	benzoyl

Any patents, patent applications, and publications cited herein are incorporated by reference.

Best Mode for Carrying out the Invention

The following Preparation and Examples are given for the purpose of illustrating the present invention in detail, but are not to be construed to limit the scope of the present invention.

Preparation 1

N-ethyl-N,N-diisopropylamine (0.174mL, 1.00mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (380 mg, 1.00 mmol) were added to a solution of 2-aminobenzamide (136 mg, 1.00 mmol) and 1-(4-phenylcyclohexyl)-3-piperidinecarboxylic acid (287 mg, 1.00 mmol) in N,N-dimethylformamide (3 mL) at room temperature. The mixture was stirred at room temperature for 6 hours. Quenched with water, and the organic materials were extracted with chloroform. The crude product was washed with methanol and chloroform to give N-[2-(aminocarbonyl)phenyl]-1-(4-phenylcyclohexyl)-3-piperidinecarboxamide (188 mg, 46.4 %) as product.

Mass (APCI): 405.93 (M^++H)

Preparation 2

The following compounds were prepared in a similar manner to that of Preparation 1.

(1) 2-({[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)-1-cyclohexen-1-yl]-carbonyl}amino)benzamide

Mass (API-ES): 402.3 (M^++H)

(2) 2-({4-[4-(3-methoxyphenyl)-3,6-dihydro-1(2H)-pyridinyl]butanoyl}-amino)benzamide

Mass (API-ES): 283.3 (M^++H)

(3) 2-({[3-(4-phenyl-1-piperidinyl)cyclohexyl]-carbonyl}amino)benzamide

Mass (APCI): 405.80 (M^++H)

Preparation 3

To a solution of 2-{[(4-oxocyclohexyl)carbonyl]amino}-benzamide (260 mg, 1.00 mmol) and 4-phenyl-1,2,3,6-

tetrahydropyridine hydrochloride (293 mg, 1.50 mmol) in tetrahydrofuran (5 mL), sodium triacetoxyborohydride (318 mg, 1.50 mmol) and acetic acid (0.086 mL, 1.50 mmol) were added at room temperature. The mixture was stirred for 15 hours, and the reaction was quenched with water. The organic materials were extracted with chloroform and dried over sodium sulfate. Purification over silica gel chromatography gave 2-({[4-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)cyclohexyl]carbonyl}amino)benzamide (266 mg, 66.0 %) as product.

Mass (API-ES): 404.4 (M^++H)

Example 1

2-{[4-(4-Phenyl-3,6-dihydro-1(2H)-pyridinyl)butanoyl]amino}benzamide (475 mg, 1.31 mmol) was dissolved in dioxane (5 mL). An aqueous solution of sodium hydroxide (1M, 3.92 mL) was added to the solution at room temperature, and the mixture was stirred at that temperature for 15 hours. The organic materials were extracted with chloroform, and the organic layer was washed with water and dried over sodium sulfate. Purification over silica gel chromatography gave cis- or trans-2-{3-[4-phenyl-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone.

Less polar product (37 mg, 38.7 %)

^{1}H NMR (200MHz, DMSO-d_6, δ): 1.4-1.8 (4H, m), 1.9-2.2 (4H, m), 2.3-2.4 (1H, m), 2.6-2.8 (4H, m), 3.0-3.2 (3H, m), 6.19 (1H, br s), 7.2-7.5 (6H, m), 7.62 (1H, d, J=7.4 Hz), 7.75 (1H, t, J=8.3 Hz), 8.07 (1H, d, J=6.6 Hz), 12.08 (1H, br s).

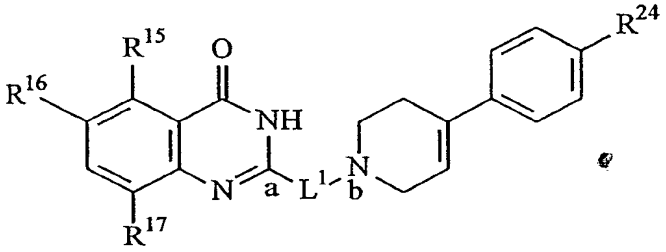
Polar one product (30 mg, 31.4 %)

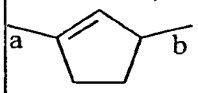
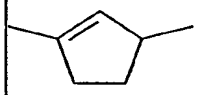
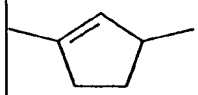
^{1}H NMR (200MHz, DMSO-d_6, δ): 1.2-1.8 (4H, m), 1.8-2.2 (4H,

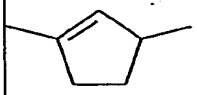
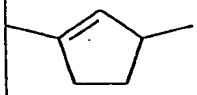
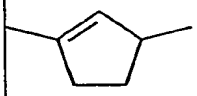
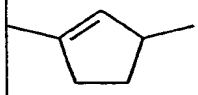
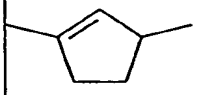
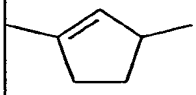
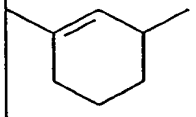
m), 2.4-2.6 (1H, m), 2.75 (2H, t, J=5.4 Hz), 3.0-3.3 (3H, m), 6.17 (1H, br s), 7.1-7.5 (6H, m), 7.59 (1H, d, J=7.8 Hz), 7.77 (1H, t, J=7.6 Hz), 8.08 (1H, d, J=7.9 Hz), 12.12 (1H, br s)

Example 2

The following compounds were prepared in a similar manner to that of Example 1.

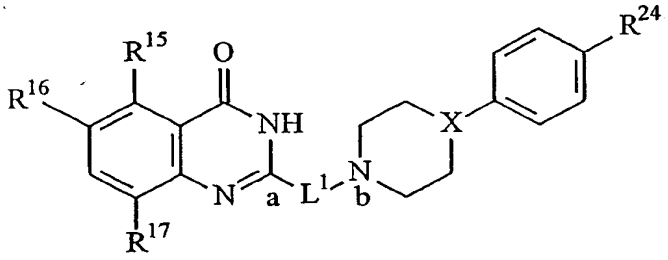


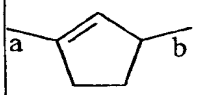
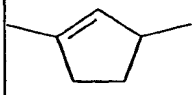
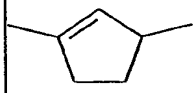
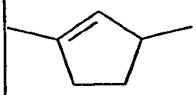
	R^{15}	R^{16}	R^{18}	R^{24}	(a)-L^1-(b)	
(1)	H	H	Me	F		^{1}H NMR (200MHz, $CDCl_3$; δ): 2.0-2.3 (2H, m), 2.62 (3H, s), 2.5-2.7 (2H, m), 2.8-3.0 (4H, m), 3.3-3.5 (2H, m), 4.18 (1H, m), 6.06 (1H, m), 6.9-7.7 (8H, m), 8.11 (1H, d, J = 7.0Hz) Mass: 402 (M^++1)
(2)	H	H	Cl	F		^{1}H NMR (200MHz, $CDCl_3$: δ) 2.0-2.3 (2H, m), 2.5-2.7 (2H, m), 2.8-3.1 (4H, m), 3.3-3.5 (2H, m), 4.18 (1H, m), 6.06 (1H, m), 6.9-7.6 (6H, m), 7.81 (1H, dd, J = 7.0Hz), 8.12 (1H, d, J = 7.0Hz) Mass: 422 (M^++1)
(3)	H	H	Cl	H		^{1}H NMR (200MHz, $CDCl_3$: δ) 2.0-2.3 (2H, m), 2.5-2.7 (2H, m), 2.8-3.1 (4H, m), 3.3-3.5 (2H, m), 4.18 (1H, m), 6.11 (1H, m), 7.0-7.6 (7H, m), 7.82 (1H, dd, J = 7.0Hz), 8.12 (1H, d, J = 7.0Hz) Mass: 404 (M^++1)

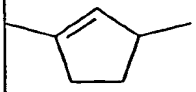
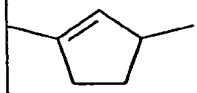
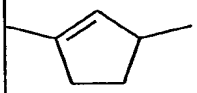
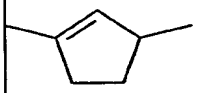
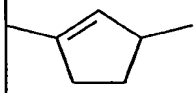
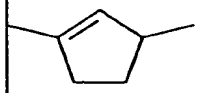
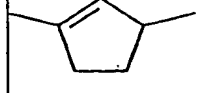
	R^{15}	R^{16}	R^{18}	R^{24}	(a)-L^1-(b)	
(4)	H	H	H	H		^{1}H NMR (200MHz, $CDCl_3$: δ) 2.0-2.3 (2H, m), 2.5-2.7 (2H, m), 2.8-3.1 (4H, m), 3.3-3.5 (2H, m), 4.18 (1H, m), 6.12 (1H, m), 7.0-7.8 (9H, m), 8.27 (1H, d, J = 7.0Hz) Mass: 370 (M^++1)
(5)	H	H	H	F		^{1}H NMR (200MHz, $CDCl_3$: δ) 2.0-2.3 (2H, m), 2.5-2.7 (2H, m), 2.8-3.1 (4H, m), 3.3-3.5 (2H, m), 4.18 (1H, m), 6.05 (1H, m), 6.9-7.5 (6H, m), 7.75 (2H, m), 8.28 (1H, d, J = 7.0Hz) Mass: 388 (M^++1)
(6)	H	Me	H	F		^{1}H NMR (200MHz, $CDCl_3$: δ) 2.0-2.3 (2H, m), 2.41 (3H, s), 2.5-2.7 (2H, m), 2.8-3.1 (4H, m), 3.3-3.5 (2H, m), 4.20 (1H, m), 6.05 (1H, m), 6.9-7.7 (7H, m), 8.06 (1H, s) Mass: 402 (M^++1)
(7)	H	Cl	H	H		^{1}H NMR (200MHz, $CDCl_3$: δ) 2.0-2.3 (2H, m), 2.5-2.7 (2H, m), 2.8-3.1 (4H, m), 3.3-3.5 (2H, m), 4.20 (1H, m), 6.07 (1H, m), 6.9-7.5 (5H, m), 7.69 (2H, s), 8.22 (1H, s) Mass: 422 (M^++1)
(8)	H	Cl	Cl	F		^{1}H NMR (200MHz, $CDCl_3$: δ) 2.0-2.3 (2H, m), 2.5-2.7 (2H, m), 2.8-3.1 (4H, m), 3.3-3.5 (2H, m), 4.20 (1H, m), 6.05 (1H, m), 6.9-7.5 (5H, m), 7.89 (1H, s), 8.14 (1H, s) Mass: 457 (M^++1)
(9)	Cl	H	Cl	H		^{1}H NMR (200MHz, $CDCl_3$: δ) 2.0-2.3 (2H, m), 2.5-2.7 (2H, m), 2.8-3.1 (4H, m), 3.3-3.5 (2H, m), 4.20 (1H, m), 6.02 (1H, m), 7.0-7.5 (6H, m), 7.71 (1H, d, J = 8.4Hz) Mass: 457 (M^++1)
(10)	H	H	H	H		^{1}H NMR (400MHz, DMSO-d_6: δ) 1.5-1.7 (2H, m), 1.84 (1H, br s), 1.96 (1H, br s), 2.35 (1H, br d, J=16.7 Hz), 2.69 (1H, d, J=17.3 Hz), 2.7-2.9 (2H, m), 3.2-3.4 (3H, m), 3.51 (1H, br s), 6.19 (1H, s), 6.98 (1H, s), 7.24 (1H, t, J=7.0 Hz), 7.34 (2H, t, J=7.6 Hz), 7.43 (2H, d, J=7.6 Hz), 7.48 (1H, t, J=7.5 Hz), 7.64 (1H, d, J=8.1 Hz), 7.79 (1H, t, J=7.7 Hz), 8.10 (1H, d, J=7.6 Hz), 12.15 (1H, br s).

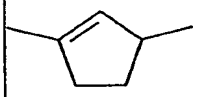
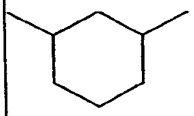
Example 3

The following compounds were prepared in a similar manner to that of Example 1.



	R^{15}	R^{16}	R^{18}	R^{24}	(a)-L^1-(b)	X	
(1)	Cl	H	Cl	H		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.4-2.5 (10H, m), 2.8-3.1 (3H, m), 4.11 (1H, m), 7.0-7.4 (9H, m), 7.71 (1H, d, J = 8.4Hz) Mass: 441 (M^++1)
(2)	H	Cl	Cl	H		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.4-2.5 (10H, m), 2.8-3.1 (3H, m), 4.09 (1H, m), 7.0-7.4 (8H, m), 7.81 (1H, m), 8.15 (1H, m) Mass: 441 (M^++1)
(3)	H	H	Cl	F		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.1 (5H, m), 2.1-2.6 (4H, m), 2.8-3.3 (4H, m), 4.05 (1H, m), 6.9-7.4 (7H, m), 7.85 (1H, d, J = 8Hz), 8.19 (1H, d, J = 8Hz) Mass: 424 (M^++1)
(4)	H	H	Cl	Cl		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.1 (5H, m), 2.1-2.6 (4H, m), 2.8-3.3 (4H, m), 4.05 (1H, m), 6.9-7.4 (7H, m), 7.82 (1H, d, J = 8Hz), 8.19 (1H, d, J = 8Hz) Mass: 441 (M^++1)
(5)	H	H	Cl	H		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.1 (5H, m), 2.1-2.6 (4H, m), 2.8-3.3 (4H, m), 4.05 (1H, m), 7.0-7.4 (7H, m), 7.82 (1H, d, J = 8Hz), 8.20 (1H, d, J = 8Hz) Mass: 406 (M^++1)

	R^{15}	R^{16}	R^{18}	R^{24}	(a)-L^1-(b)	X	
(6)	H	H	Me	F		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.1 (5H, m), 2.1-2.6 (4H, m), 2.8-3.3 (4H, m), 4.05 (1H, m), 6.8-7.4 (6H, m), 7.60 (1H, d, J = 8Hz), 8.14 (1H, d, J = 8Hz) Mass: 404 (M^++1)
(7)	H	H	Me	Cl		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.1 (5H, m), 2.1-2.6 (4H, m), 2.8-3.3 (4H, m), 4.05 (1H, m), 6.8-7.4 (6H, m), 7.60 (1H, d, J = 8Hz), 8.14 (1H, d, J = 8Hz) Mass: 420 (M^++1)
(8)	H	Me	H	F		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.1 (5H, m), 2.1-2.6 (4H, m), 2.44 (3H, s), 2.8-3.3 (4H, m), 4.05 (1H, m), 7.0-7.4 (6H, m), 7.5-7.7 (2H, m), 8.08 (1H, s) Mass: 386 (M^++1)
(9)	H	Cl	H	H		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.1 (5H, m), 2.1-2.6 (4H, m), 2.44 (3H, s), 2.8-3.3 (4H, m), 4.05 (1H, m), 7.0-7.4 (6H, m), 7.6-7.7 (2H, m), 8.24 (1H, s) Mass: 406 (M^++1)
(10)	H	Cl	H	Cl		CH	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.1 (5H, m), 2.1-2.6 (4H, m), 2.44 (3H, s), 2.8-3.3 (4H, m), 4.05 (1H, m), 7.0-7.4 (5H, m), 7.6-7.8 (2H, m), 8.24 (1H, s) Mass: 441 (M^++1)
(11)	H	H	Me	Cl		N	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.2 (2H, m), 2.62 (3H, m), 2.7-3.3 (12H, m), 4.08 (1H, m), 6.7-6.9 (3H, m), 7.1-7.3 (3H, m), 7.60 (1H, d, J = 8Hz), 8.13 (1H, d, J = 8Hz) Mass: 421 (M^++1)
(12)	H	H	Me	F		N	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.2 (2H, m), 2.62 (3H, m), 2.7-3.3 (12H, m), 4.06 (1H, m), 6.8-7.3 (6H, m), 7.59 (1H, d, J = 8Hz), 8.14 (1H, d, J = 8Hz) Mass: 405 (M^++1)
(13)	H	H	Cl	F		N	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.2 (2H, m), 2.7-3.3 (12H, m), 4.06 (1H, m), 6.8-7.3 (6H, m), 7.81 (1H, d, J = 8Hz), 8.21 (1H, d, J = 8Hz) Mass: 425 (M^++1)

	R^{15}	R^{16}	R^{18}	R^{24}	(a)-L^1-(b)	X	
(14)	H	H	H	Cl		N	^{1}H NMR (200MHz, $CDCl_3$: δ) 1.8-2.2 (2H, m), 2.62 (3H, m), 2.7-3.3 (12H, m), 4.08 (1H, m), 6.8-7.0 (2H, d, J = 8Hz), 7.09 (1H, m), 7.21 (2H, d, J = 8Hz), 7.45 (1H, t, J = 8Hz), 7.61 (1H, d, J = 8Hz), 7.75 (1H, t, J = 8Hz), 8.09 (1H, d, J = 8Hz) Mass: 407 (M^++1)
(15)	H	H	H	H		CH	^{1}H NMR (200MHz, DMSO-d_6: δ) 1.4-2.3 (14H, m), 3.0-3.5 (5H, m), 7.1-7.4 (5H, m), 7.46 (1H, t, J=7.6 Hz), 7.62 (1H, d, J=7.4 Hz), 7.78 (1H, t, J=7.6 Hz), 8.08 (1H, d, J=6.6 Hz), 12.12 (1H, br s) Mass (APCI) 387.73 (M^++H)

Example 4

The following compound was prepared in a similar manner to that of Example 1.

(1) 2-[1-(4-Phenylcyclohexyl)-3-piperidinyl]-4(3H)-quinazolinone

^{1}H NMR (200MHz, $CDCl_3$: δ): 1.6-2.3 (13H, m), 2.4-2.6 (2H, m), 2.84 (1H, sept., J=3.8 Hz), 3.09 (1H, br s), 3.18 (1H, br d, J=10.7 Hz), 3.32 (1H, br d, J=11.9 Hz), 7.1-7.5 (6H, m), 7.62 (1H, d, J=7.0 Hz), 7.71 (1H, t, J=6.8 Hz), 8.29 (1H, d, J=8.0 Hz), 12.87 (1H, br s)

Mass (APCI): 388.20 (M^++H).

Example 5

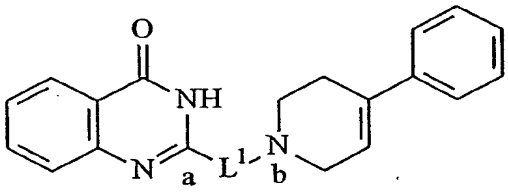
Triethylamine (1.54 mL, 11.1 mmol) was added to a suspension of 2-chloro-4(3H)-quinazolinone (100 mg, 0.554 mmol) and 2-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)ethanamine dihydrochloride (229 mg, 0.831 mmol) in N,N-dimethylformamide (3 mL), and the mixture was heated at 100°C for 3 hours. Cooled to

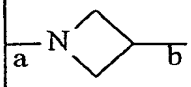
room temperature, and the reaction were quenched with water, and the product was extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. Purification over silica gel chromatography gave 2-{[2-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)ethyl]amino}-4(3H)-quinazolinone (76 mg, 39.6 %) as product.

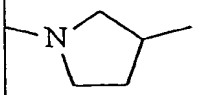
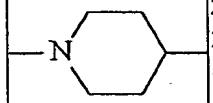
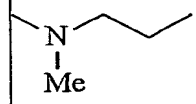
^{1}H NMR (400MHz, DMSO-d_6: δ): 2.51 (2H, br s), 2.64 (2H, t, J=6.0 Hz), 2.71 (2H, t, J=5.6 Hz), 3.17 (2H, d, J=3.1 Hz), 3.51 (2H, q, J=5.5 Hz), 6.18 (1H, t, J=3.5 Hz), 6.36 (1H, br s), 7.10 (1H, t, J=7.5 Hz), 7.2-7.3 (2H, m), 7.34 (2H, t, J=6.5 Hz), 7.44 (2H, d, J=7.2 Hz), 7.56 (1H, t, J=7.7 Hz), 7.87 (1H, dd, J=7.9, 1.4 Hz), 11.05 (1H, br s)

Example 6

The following compounds were prepared in a similar manner to that of Example 5.



	(a)-L^1-(b)	
(1)		^{1}H NMR (400MHz, DMSO-d_6: δ): 2.60 (2H, t, J=5.5 Hz), 3.0-3.1 (2H, m), 3.3-3.4 (1H, m), 3.98 (2H, dd, J=9.0, 5.2 Hz), 4.18 (2H, t, J=8.0 Hz), 6.17 (1H, br s), 7.13 (1H, t, J=7.5 Hz), 7.24 (1H, t, J=7.2 Hz), 7.27 (1H, d, J=7.6 Hz), 7.34 (2H, t, J=7.6 Hz), 7.43 (2H, d, J=7.3 Hz), 7.57 (1H, t, J=7.7 Hz), 7.90 (1H, dd, J=7.9, 1.5 Hz), 11.45 (1H, br s)

	(a)-L^1-(b)	
(2)		^{1}H NMR (400MHz, DMSO-d_6: δ): 1.86 (1H, quint., J=10.5 Hz), 2.24 (1H, quint., J=5.7 Hz), 2.6-2.8 (2H, m), 3.01 (1H, quint., J=7.5 Hz), 3.19 (2H, q, J=9.6 Hz), 3.3-3.4 (3H, m), 3.46 (1H, dt, J=10.4, 6.8 Hz), 3.75 (1H, t, J=8.8 Hz), 3.90 (1H, dd, J=10.4, 7.0 Hz), 6.17 (1H, br s), 7.09 (1H, t, J=7.3 Hz), 7.2-7.3 (2H, m), 7.34 (2H, t, J=7.6 Hz), 7.44 (2H, d, J=7.3 Hz), 7.55 (1H, t, J=7.6 Hz), 7.89 (1H, dd, J=7.9, 1.5 Hz), 11.00 (1H, br s)
(3)		^{1}H NMR (400MHz, DMSO-d_6: δ): 1.48 (2H, q, J=11.7 Hz), 1.88 (2H, d, J=11.9 Hz), 2.45 (2H, br s), 2.58 (1H, t, J=5.5 Hz), 2.73 (2H, t, J=5.5 Hz), 2.94 (2H, t, J=11.9 Hz), 3.23 (2H, d, J=2.7 Hz), 4.43 (2H, br d, J=13.1 Hz), 6.15 (1H, br s), 7.13 (1H, t, J=7.0 Hz), 7.23 (1H, t, J=7.2 Hz), 7.2-7.4 (2H, m), 7.41 (2H, d, J=7.3 Hz), 7.57 (1H, t, J=7.7 Hz), 7.89 (1H, dd, J=7.9, 2.9 Hz), 11.26 (1H, br s)
(4)		^{1}H NMR (400MHz, DMSO-d_6: δ): 2.55 (2H, br s), 2.69 (2H, t, J=5.8 Hz), 2.79 (2H, t, J=5.6 Hz), 3.12 (3H, s), 3.23 (2H, d, J=3.0 Hz), 3.69 (2H, t, J=5.6 Hz), 6.14 (1H, br s), 7.08 (1H, t, J=7.5 Hz), 7.2-7.3 (2H, m), 7.33 (2H, t, J=7.8 Hz), 7.42 (2H, d, J=7.2 Hz), 7.5-7.6 (1H, m), 7.85 (1H, dd, J=7.9, 1.5 Hz)

Example 7

The following compound was prepared in a similar manner to that of Example 4.

(1) 2-[[2-(Dimethylamino)ethyl](methyl)amino]-4(3H)-quinazolinone

^{1}H NMR (400MHz, DMSO-d_6: δ): 2.87 (6H, s), 3.22 (3H, s), 3.3-3.4 (2H, m), 3.94 (2H, t, J=5.9 Hz), 7.15 (1H, t, J=7.6 Hz), 7.30 (1H, br), 7.60 (1H, t, J=7.6 Hz), 7.91 (1H, d, J=7.8 Hz)

Example 8

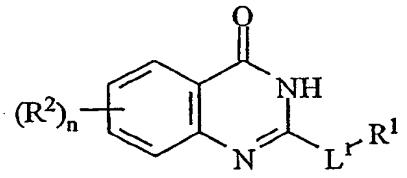
Triethylamine (1.40 mL, 10.0 mmol) was added to a suspension

of 2-chloro-4(3H)-quinazolinone (181 mg, 1.00 mmol) and N,N-dimethyl-1,2-ethanediamine (0.196 mL, 1.50 mmol) in dioxane (5 mL), and the mixture was heated at reflux for 2 hours. Cooled to room temperature, and the reaction were quenched with water, and the product was extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. Purification over silica gel chromatography and treatment of the product with a solution of hydrogen chloride in ethyl acetate (4M, 1 mL) gave 2-{[2-(dimethylamino)ethyl]amino}-4(3H)-quinazolinone hydrochloride (141 mg, 52.3 %) as product.

^{1}H NMR (400MHz, DMSO-d_6: δ): 2.86 (6H, s), 3.36 (2H, br), 4.00 (2H, br d, J=4.5 Hz), 7.36 (1H, t, J=8.0 Hz), 7.7-7.9 (2H, m), 8.00 (1H, d, J=7.9 Hz), 8.5 (1H, br), 10.46 (1H, br)

C L A I M S

1. A compound of the formula (I):



(I)

wherein R^1 is substituted cyclic amino groups, optionally substituted carbocyclic group or optionally substituted amino group,

R^2 is substituent,

n means an integer of 0 to 4, and

L^1 is (1) cyclo(lower)alkylene, (2) cyclo(lower)alkenylene, (3) diradical of saturated- or unsaturated monocyclic group with one or more nitrogen atom(s), which is obtained after removal of one hydrogen atom from said monocyclic group, or (4) $-N(R^3)-L^2-$ (wherein R^3 is hydrogen or lower alkyl, and L^2 is lower alkylene or lower alkenylene),

or its prodrug, or a salt thereof.

2. The compound according to claim 1, wherein

R^2 is halogen, lower alkyl or lower alkoxy.

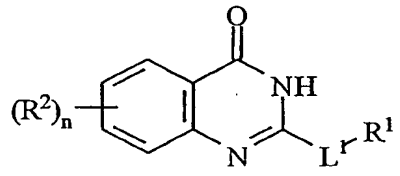
3. The compound according to claim 2, wherein

R^1 is (1) cyclic amino group substituted with aryl optionally substituted with halogen, lower alkoxy, lower alkyl or halo(lower)alkyl, or (2) lower alkylamino.

4. The compound according to claim 3, wherein
R^1 is tetrahydropyridyl, piperidyl or piperazinyl, each of which is substituted with aryl optionally substituted with halogen.

5. The compound according to any one of claims 2, 3, 4 and 5, wherein
L is cyclo(lower)alkylene or cyclo(lower)alkenylene.

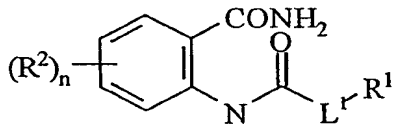
6. A process for preparing a compound of the formula (I):



(I)

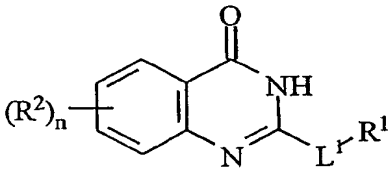
wherein R^1 is substituted cyclic amino groups, optionally substituted carbocyclic group or optionally substituted amino group,
R^2 is substituent,
n means an integer of 0 to 4, and
L^1 is (1) cyclo(lower)alkylene, (2) cyclo(lower)alkenylene, (3) diradical of saturated- or unsaturated monocyclic group with one or more nitrogen atom(s), which is obtained after removal of one hydrogen atom from said monocyclic group, or (4) $-N(R^3)-L^2-$ (wherein R^3 is hydrogen or lower alkyl, and L^2 is lower alkylene or lower alkenylene),
or its prodrug, or a salt thereof,
which comprises,

(1) subjecting the compound of the following formula (II):



(II)

or a salt thereof, to cyclization reaction in the presence of base to provide a compound of the formula (I):



(I)

or a salt thereof, in the above formulae,
R^1, R^2, n and L^1 are each as defined above.

7. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or its prodrug, or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

8. A compound of claim 1 or its prodrug, or a pharmaceutically acceptable salt thereof for use as a medicament.

9. A pharmaceutical composition of claim 7 for inhibiting PARP activity.

10. A pharmaceutical composition of claim 7 for treating or preventing diseases ascribed by NMDA- and NO-induced toxicity.

11. A pharmaceutical composition of claim 7 for extending the lifespan or proliferative capacity of cells or altering gene expression of senescent cells.

12. A method for treating or preventing tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke; Alzheimer's disease; Parkinson's disease; epilepsy; Amyotrophic Lateral Scleosis (ALS); Huntington's disease; schizophrenia; chronic pain; ischemia and nloss following hypoxia; hypoglycemia; ischemia; trauma; nervous insult; previously ischemic heart or skeleton muscle tissue; radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy; skin aging; arteriosclerosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescence diseases; inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and tumor, which comprises administering a compound of claim 1 or its prodrug, or a pharmaceutically acceptable salt thereof to a human being or an animal.

13. A use of a compound of claim 1 or its prodrug, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

INTERNATIONAL SEARCH REPORT

.... ational Application No
PCT/JP 02/13286

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/88 A61K31/517 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 24379 A (CANCER RES CAMPAIGN TECH ;GRIFFIN ROGER JOHN (GB); CALVERT ALAN HI) 14 September 1995 (1995-09-14) cited in the application page 3, formula II page 6, line 32 -page 7, line 7 Table III, Compounds no. NU1063, NU1065, NU1069	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 2003	17/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hoepfner, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/13286

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-13 (part)

Provision of a quinazoline derivative of formula (I) having at position 2 a saturated or unsaturated carbocycle substituted with a further substituent selected from a nitrogen-containing heterocycle, a carbocycle or an amino group, a method for its preparation and its medical use.

2. Claims: 1-13 (part)

Provision of a quinazoline derivative of formula (I) having at position 2 a saturated or unsaturated nitrogen-containing heterocycle substituted with a further substituent selected from a nitrogen-containing heterocycle, a carbocycle or an amino group, a method for its preparation and its medical use.

3. Claims: 1-13 (part)

Provision of a quinazoline derivative of formula (I) having at position 2 an amino group having an alkyl substituent being substituted with a further substituent selected from a nitrogen-containing heterocycle, a carbocycle or an amino group, a method for its preparation and its medical use.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/13286

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9524379 A	14-09-1995	AT 184271 T	15-09-1999
		AT 210651 T	15-12-2001
		AT 231494 T	15-02-2003
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		ES 2169472 T3	01-07-2002
		WO 9524379 A1	14-09-1995
		GR 3031886 T3	29-02-2000
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		US 6316455 B1	13-11-2001
		US 5756510 A	26-05-1998